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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/917,791	07/31/2001	Mark Dertzbaugh		9485

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	11

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/917,791	Applicant(s) DERTZBAUGH, MARK	
	Examiner Jennifer E. Graser	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted 9/3/03, Paper No. 10B is made. Claims 2-8 are currently pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 2-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-8 are vague and indefinite because the claims do not contain the sequence identifier which places the recited domains in relation to the entire protein. When a specific domain is identified by amino acid number, the sequence to which it refers must be included in the claims. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. Applicants have argued that the position is identified in accord with usual practice and

refers to a contiguous sequence from a larger sequence. This has been fully and carefully considered, but is not deemed persuasive in overcoming the rejection. The problem lies in the fact that claim 2 does not identify the larger sequence by sequence identifier. Accordingly it is unclear how the domains relate to the entire protein. When referring to specific amino acids, a reference sequence by sequence identifier must be included in the claim.

Claims 2 and 3 refer both to cancelled claim 1 and new claim 8. The reference to cancelled claim 1 must be removed from the claims.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 8 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Binz et al. (J.Biol.Chem, 265(16): 9153-9158. 1990).

Binz et al teach the complete amino acid sequence of the botulinum neurotoxin type A. This sequence has at least 100% identical amino acids from domains $H_{455\text{-}661}$ and $H_{1150\text{-}1289}$, i.e., Applicant's SEQ ID Nos: 21 and 22, respectively. The current claim language "consisting of at least" is open language which encompasses the entire neurotoxin. In order to overcome the rejection the claims must be amended to recite "an isolated polypeptide *consisting of* SEQ ID NO:21 or SEQ ID NO:22". The requirement of *at least* 100 amino acids from SEQ ID NO:21 or

22 would still read on the full-length sequence because it still allows for more than the 100 amino acids, i.e., the other 1195/6 amino acids. A pharmaceutically acceptable carrier reads on water and is inherent in the preparation/isolation of the polypeptide disclosed by Binz. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Response to Applicants' Arguments:

Applicants argue that they are claiming a smaller sequence from the full-length neurotoxin with a particular activity, i.e., protective immunity. The argue that the claims are not anticipated by the longer sequence which does not provide the advantages of the claimed invention. This has been fully and carefully considered but is not deemed persuasive. The current claim language "consisting of at least" is open language which encompasses the entire neurotoxin. Further, the toxin of Binz is, in fact, detoxified. The claims are not limited to the specific domains due to the phrase "at least". The claims encompass much more than 100 amino acids from either domain, i.e, they read on the full-length neurotoxin taught by Binz. The claims do not require the polypeptide to have any particular activity or characteristics. Further, if the claims are intended to encompass unexpected results then the claim must be written to encompass the composition which achieves the unexpected results, i.e., limited to a specific size.

5. Claims 2 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Thompson et al. (Gencore Accession NO. S09492 which corresponds to Eur. J.Biochem. 189,:73-81, 1990).

Thompson et al teach the complete amino acid sequence of the Clostridium botulinum type A neurotoxin sequence which has at least 100% identical amino acids from domains $H_{455-661}$ and $H_{1150-1289}$, i.e., Applicant's SEQ ID Nos: 21 and 22, respectively. The current claim language "consisting at least" is open language which encompasses the entire neurotoxin. In order to overcome the rejection the claims must be amended to recite "an isolated polypeptide *consisting of* SEQ ID NO:21 or SEQ ID NO:22". The requirement of *at least* 100 amino acids from SEQ ID NO:21 or 22 would still read on the full-length sequence because it still allows for more than the 100 amino acids, i.e., the other 1195/6 amino acids. The composition of matter recited in claim 2 comprises only the polypeptide. This is structurally the same as the polypeptide taught by Binz et al. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Response to Applicants' Arguments:

Applicants argue that they are claiming a smaller sequence from the full-length neurotoxin with a particular activity, i.e., protective immunity. They argue that Thompson provides no direction on how to choose a smaller sequence. They argue that the claims are not anticipated by the longer sequence which does not provide the advantages of the claimed

invention. This has been fully and carefully considered but is not deemed persuasive. The current claim language "consisting at least" is open language which encompasses the entire neurotoxin. Further, the toxin of Binz is, in fact, detoxified. The claims are not limited to the specific domains due to the phrase "at least". The claims encompass much more than 100 amino acids from either domain, i.e, they read on the full-length neurotoxin taught by Thompson. The claims do not require the polypeptide to have any particular activity or characteristics. Further, if the claims are intended to encompass unexpected results then the claim must be written to encompass the composition which achieves the unexpected results, i.e., limited to a specific size. The issue isn't whether Thompson gives direction to choosing a smaller sequence. The issue is that the claims are not limited to a smaller sequence.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Binz et al J.Biol.Chem, 265(16): 9153-9158. 1990) in view of Lang (EP 562132 A1) and further in view of Lockman et al. (J.Biol.Chem. 258(22): 13722-13725, 1983).

The teachings of Binz et al are set forth above. However, they do not particularly exemplify linking said polypeptides with the A2 peptide of cholera or any other polypeptide which acts as an adjuvant.

Lang teaches antibodies to the A fragments of related tetanus toxin.

Lockman et al teach a method of fusing or joining a polypeptide with the A2 peptide of cholera toxin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a polypeptide comprising the neurotoxin of *C.botulinum* linked to the A2 peptide of cholera toxin because Binz and Thompson teach a detoxified botulinum toxin A which has at least 100 amino acids from domains $H_{455\text{-}661}$ and $H_{1150\text{-}1289}$ and Lockman specifically teaches fusing a polypeptide with the A2 peptide of cholera toxin. Since Binz has suggested detoxified neurotoxin of *C.botulinum* to be a good candidate for a safe vaccine composition (see page 9153, first paragraph) and has shown that said detoxified toxin is immunogenic as demonstrated by the production of polyclonal and monoclonal antibodies (see page 9154, paragraph bridging columns 1-2) it would have been obvious to use it as a vaccine in methods of immunizing mammals susceptible to botulism. Further, since cholera toxin was a well known adjuvant/carrier at the time the invention was made, it would have been obvious to one of ordinary skill in the art to prepare polypeptide compositions or fusion proteins of *C.botulinum* neurotoxin and A2 peptide of Cholera toxin in order to provide a safe vaccine which would provide enhanced immunogenicity over a vaccine comprising *C.botulinum* neurotoxin alone.

Additionally, Binz et al teach that both botulinum neurotoxin A and tetanus A fragments have similar functions (see page 9153, para. 1, lines 27-30) and Lang teaches that antibodies to A fragments of the tetanus toxin are useful for protection. The prior art teaches that most toxins are in fact protective because antibodies raised against the toxins protect from cellular effects of the toxin by binding the toxin and removing it from circulation. A detoxified toxin would be expected to be both immunogenic and protective. However, it is noted that the instant claims do not require protection. In addition, the instant toxin bears a strong degree of identity to other homologous toxins which have been found to be protective when detoxified (i.e., tetanus toxin, see page 9158, col.1, first full paragraph). The addition of A2 peptide from cholera would be expected to enhance immunogenicity to the *C.botulinum* neurotoxin in an additive or cumulative manner.

Response to Applicant's Arguments:

As stated above, the claims are not limit to smaller sequences. The issue isn't, as Applicants argue, whether Binz or Thompson give direction to choosing a smaller sequence. The issue is that the instant claims are not limited to said smaller sequence.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.